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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,008	05/06/2002	Steven K Libutti	14014.0322U2	3848

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EXAMINER	
BURKHART, MICHAEL D	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
09/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/031,008	LIBUTTI ET AL.	
	Examiner	Art Unit	
	Michael Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-19,22-37,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *3,5-15,17,19,23-37 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4, 16, 18, 22 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/7/2009 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 4, 16, 18, 22 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al (U.S. patent 6,638,502, of record) in view of Restifo et al (U.S. patent 5,733,548, of record). **This rejection is maintained for reasons made of record in the Office Actions dated**

2/22/2006, 11/9/2006, 6/13/2007, 2/8/2008, 11/13/2008, 4/8/2009, and for reasons set forth below.

Response to Arguments

Applicants present no new arguments in the response filed 8/7/2009. Presuming the most recent RCE was filed in order to have the documents cited on the most recent IDS considered, applicant's arguments dated 2/17/2009 and answered in the Advisory Action dated 4/8/2009 are reiterated below.

Applicant's arguments filed 2/17/2009 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) the results of the instant invention are surprising in light of the teachings of Gabathuler et al regarding the E3/19K protein; 2) Restifo et al involve targeting a peptide to the ER in order to associate it with MHC molecules, producing a complex that is displayed on the cell surface and thus not secreted; 3) the art does not hint that proteins attached to an E19 signal sequence would be secreted; 4) Li et al teach that the signal sequence is not the E19 signal sequence; 5) the present rejection is based upon the assumption that all signal sequences are the same, which is contradicted by the prior art; 6) Neither Restifo nor Li et al teach that the E19 signal sequence will predictably express a secreted form of an antiangiogenic protein commensurate in scope with the claims; 7) nothing in the prior art suggest arriving at a composition that reduces tumor growth when administered systemically; 8) Griscelli et al does make up for the deficiencies of Restifo and Li et al.

Regarding 1), Gabathuler et al teaches that the E3/19K protein has an ER retention signal at the carboxy terminus responsible for its retention in the ER and a signal sequence at the amino terminus (see the abstract and page 1803). The claims are not directed to an intact E3/19K

protein comprising an ER retention signal, nor is the prior art of record, which use the signal sequence only, located at the opposite end of the intact E3/19K protein. Therefore, the function of such a protein in nature to sequester MHC molecules in the secretory pathway (emphasis added) does not mitigate against the rejection in light of the prior art teachings made of record and discussed extensively in previous Office Actions.

Regarding 2), peptides associated with MHC molecules are broadly considered "secreted", despite applicants assertions and protests to the contrary. This is because they are processed through the same general secretory pathway (i.e. ER, Golgi, etc. See Alberts et al, pages 599-601) as all molecules ultimately bound for what is considered "outside" the cell. The only reason MHC molecules remain bound to the cell are their transmembrane domains, which serve as an anchor (see Fig. 4.11 from Janeway et al for an illustration). Molecules without such a transmembrane domain are released from the cell into the surrounding milieu.

Regarding 3), this statement is false on its face. As detailed by the prior art made of record, the very purpose of signal sequences are to direct proteins to the secretory pathway. Applicants offer no alternative explanation as to why a signal sequence would exist other than to direct a protein to some component of the secretory pathway. Applicants are not the first to measure secretion mediated by the E19 signal sequence for reason of record, i.e. the teachings of Restifo et al. Because the peptide:MHC complexes of Restifo et al remain attached to the cell surface does not mean they are not secreted, as applicants mistakenly assert, see the explanation above. Applicants further ignore the evidence that antiangiogenic proteins can be expressed and secreted using signal sequences other than those "naturally" associated with the antiangiogenic

protein, and that such relatively large proteins are not bound by MHC molecules (which bind small peptides, not proteins).

Regarding 4), a review of Li et al reveals no such statement.

Regarding 5), a review of the prosecution of this application reveals no such statement by the Examiner. The art cited by applicants asserted to teach the unpredictability of signal sequences (Hegde et al) supports the predictability of using such sequences. That certain signal sequences have different efficiencies in various cell types is not surprising given the breadth of possible signal sequences, the proteins they are naturally associated with, and the breadth of cells and organisms they are derived from. This does not speak to the predictability of using the instantly claimed signal sequence, which is to be used in the very organism it has evolved to be effective in (humans) and has been shown to be effective in directing secretion of exogenous peptides. A review of Hegde et al reveals nothing to refute this. Regarding Martoglio et al, it is not clear, and applicants do not explain, why the discussion of signal sequences and their efficiency mitigates against the instant rejection, which involves an adenoviral ss which has evolved to be functional in human cells, and is evidenced by the art of record to secrete heterologous proteins.

Regarding 6), this is, again, a statement of opinion that is false on its face and completely ignores the facts and evidence found in the teachings of Restifo and Li et al. The E19 signal sequence, again, was used to direct expression and secretion of given peptides, even if said peptides were in a complex with MHC molecules that remain bound to the cell surface. See the explanation above. An extensive analysis of why the combination of Li and Restifo et al meet the intended use limitations of claim 40 has been provided, i.e. the compound rendered obvious

by these references would provide increased levels of an antiangiogenic protein relative to situations wherein no compound is administered, and such antiangiogenic proteins are known in the art to reduce tumor growth. There is nothing surprising about a known antiangiogenic protein reducing tumor growth when administered to a tumor or an animal having a tumor.

Regarding 7), again, this is an intended use limitation and has been addressed previously. Applicants present a paragraph of arguments regarding this issue, but nothing in these arguments details what exactly the structural limitation imposed by this intended use might be. These arguments are also silent regarding how the asserted "functional" limitation is to be interpreted into a structural limitation other than those limitations already addressed by the Examiner. The composition taught by the prior art meets all the structural limitations of the claims, and thus meets the intended use limitation. A "reasonable expectation of success" is not a structural limitation, but rather is a policy consideration in 35 USC 103 rejections. Given the highly advanced state of the art, and the lack of a basis of comparison (see below), it has been considered throughout prosecution that a reasonable expectation of success is present. Applicants have confused this standard with an absolute certainty of success, which does not appear to be a possibility in 35 USC 103 rejections. Absent evidence to the contrary, the use of the adenoviral E19 ss sequence to express an antiangiogenic protein in the context of an adenoviral vector would result in increased levels of circulating antiangiogenic protein relative to organisms/animals that did not receive the adenoviral vector, or received a control vector not expressing the antiangiogenic protein. The results of Griscelli et al, and applicants Exhibit C (submitted with the Pasqualini declaration, 12/14/2007), page 1018, third column, first full ,

teach the general reduction in tumor size upon administration of viral vectors expressing antiangiogenic proteins.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Burkhart whose telephone number is (571)272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Burkhart/
Primary Examiner, Art Unit 1633